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Date: December 8, 2003

Practitioner's Docket No. MPI94-008CP2DV2CN5M

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: Julian Adams, et al.

Divisional N/A

Group No.: N/A

Application No.:

Filed: December 8, 2003

Examiner: N/A

For: BORONIC ESTER AND ACID COMPOUNDS, SYNTHESIS AND USES

Mail Stop Patent Application

Commissioner for Patents

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**INFORMATION DISCLOSURE STATEMENT**

**List of Sections Forming Part of This Information Disclosure Statement**

The following sections are being submitted for this Information Disclosure Statement:

1. [x] Preliminary Statements;
2. [x] Forms PTO/SB/08A and 08B (substitute for Form PTO-1449);
3. [x] Identification of Prior Application in Which Listed Information Was Already Cited and for Which No Copies Are Submitted or Need Be Submitted (AA-AV, BA-BBB, CA-CCA)

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**Preliminary statements**

Applicants submit herewith patents, publications or other information, of which they are aware that they believe may be material to the examination of this application, and in respect of which, there may be a duty to disclose.

The filing of this information disclosure statement shall not be construed as a representation that a search has been made (37 C.F.R. section 1.97(g)), an admission that the information cited is, or is considered to be, material to patentability, or that no other material information exists.

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**Identification of Prior Application in Which Listed Information Was Already Cited  
and for Which No Copies Are Submitted or Need Be Submitted**

This application relies, under 35 U.S.C. section 120, on the earlier filing date of prior application Serial No. 10/392,165, filed on March 19, 2003.

The cited references were submitted to, and/or cited by, the Office in the prior application(s) and, therefore, are not required to be provided in this application. However, the undersigned will provide additional copies upon request.

December 8, 2003

Respectfully submitted,  
MILLENNIUM PHARMACEUTICALS, INC.

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Substitute for form 1449A/PTO				<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				Application Number	Not yet Assigned
				Filing Date	December 8, 2003
				First Named Inventor	Julian Adams, et al.
				Group Art Unit	N/A
				Examiner Name	N/A
(use as many sheets as necessary)				Attorney Docket Number	MPI94-008CP2DV2CN5M
Sheet	1	of	2		

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document (MM-DD-YYYY)	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
	AA	5,187,157		Kettner, et al.	02-16-1993	Entire document
	AB	5,250,720		Kettner, et al.	10-05-1993	Entire document
	AC	5,106,948		Kinder, et al.	04-21-1992	Entire document
	AD	5,424,904		Kettner, et al.	09-07-1993	Entire document
	AE	6,066,730		Adams, et al.	05-02-2000	Entire document
	AF	5,780,454		Adams, et al.	07-00-1998	Entire document
	AG	6,083,903		Adams, et al.	07-00-2000	Entire document
	AH	5,574,017		Gutheil	11-12-1996	Entire document
	AI	5,990,083		Iqbal, et al.	11-23-1999	Entire document
	AJ	4,261,868		Hora, et al.	04-14-1981	Entire document
	AK	4,369,183		Jones, et al.	01-18-1983	Entire document
	AL	4,499,082		Shenvi, et al.	02-12-1985	Entire document
	AM	4,537,707		Severson, R. Jr.	08-27-1985	Entire document
	AN	4,537,773		Shenvi, A.	08-27-1985	Entire document
	AO	4,842,769		Shulman, et al.	06-27-1989	Entire document
	AP	4,963,655		Kinder, et al.	10-16-1990	Entire document
	AQ	4,997,929		Collins, et al.	03-05-1991	Entire document
	AR	5,030,378		Venegas, M.	07-09-1991	Entire document
	AS	5,169,841		Kleeman, et al.	12-08-1992	Entire document
	AT	5,550,262		Iqbal, et al.	08-27-1996	Entire document
	AU	5,614,649		Iqbal, et al.	03-25-1997	Entire document
	AV	4,510,130		Platt, et al.	04-09-1985	Entire document

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document (MM-DD- YYYY)	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Code <sup>5</sup> Office <sup>3</sup> (known)	Kind Number <sup>4</sup>	(if known)				
	BA	WO	93/01828			02-04-1993	Entire document.	
	BB	EP	0 315 574			05-10-19989	Entire document.	
	BC	WO	95/25533			09-28-1995	Entire document.	
	BD	WO	95/24914			09-21-1995	Entire document.	
	BE	EP	0 145 441			06-19-1985	Entire document.	
	BF	EP	0 293 881			12-07-1988	Entire document.	
	BG	WO	88/10266			12-29-1988	Entire document.	

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		<b>Applicant Number</b>	Not yet Assigned		
		<b>Filing Date</b>	December 8, 2003		
		<b>First Named Inventor</b>	Julian Adams, et al.		
		<b>Group Art Unit</b>	N/A		
		<b>Examiner Name</b>	N/A		
<b>Sheet</b>	2	<b>of</b>	2	<b>Attorney Docket Number</b>	MPI94-008CP2DV2CN5M

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		Code <sup>5</sup> Office <sup>3</sup> <i>known</i> )	Kind Number <sup>4</sup>	(if				
	BH	EP	0 354 522			02-14-1990	Entire document.	
	BI	DE	38 27 340			02-15-1990	Entire document.	
	BJ	EP	0 363 284			04-11-1990	Entire document.	
	BK	EP	0 364,344			04-18-1990	Entire document.	
	BL	EP	0 381 262			08-08-1990	Entire document.	
	BM	EP	0 393 457			10-24-1990	Entire document.	
	BN	WO	91/13904			09-19-1991	Entire document.	
	BO	EP	0 471 651			02-19-1992	Entire document.	
	BP	EP	0 478 050			04-01-1992	Entire document.	
	BQ	WO	92/07869			05-14-1992	Entire document.	
	BR	WO	92/11850			07-23-1992	Entire document.	
	BS	WO	92/12140			07-23-1992	Entire document.	
	BT	EP	0 511 456			11-04-1992	Entire document.	
	BU	WO	92/19707			11-12-1992	Entire document.	
	BV	WO	92/19709			11-12-1992	Entire document.	
	BW	WO	93/21213			10-28-1993	Entire document.	
	BX	WO	93/21214			10-28-1993	Entire document.	
	BY	EP	0 583 536			02-23-1994	Entire document.	
	BZ	WO	94/21668			09-29-1994	Entire document.	
	BBA	WO	94/23045			10-13-1994	Entire document.	
	BBB	WO	95/09858			04-13-1995	Entire document.	

<b>Examiner Signature</b>		<b>Date Considered</b>	

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		Filing Date	December 8, 2003
		First Named Inventor	Julian Adams, et al.
		Group Art Unit	N/A
		Examiner Name	N/A
		Attorney Docket Number	MPI94-008CP2DV2CN5M
Sheet	1	of	3

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	CA	Aoyagi, T. et al., "Structures and Activities of Protease Inhibitors of Microbial Origin," <i>Proteases and Biological Control</i> , Vol. 2, Reich, E., et al., eds., Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, pp. 429-454 (1975).	
	CB	Bachovchin, W., et al., "Nitrogen-15 NMR Spectroscopy of the Catalytic-Triad Histidine of a Serine Protease in Peptide Boronic Acid Inhibitor Complexes," <i>Biochem.</i> Vol. 27, pp. 7689-7697 (1988).	
	CD	Berry, S., et al., "Interaction of Peptide Boronic Acids with Elastase: Circular Dichroism Studies," <i>Proteins: Structure, Function, and Genetics</i> , Vol. 4, pp. 205-210 (1988).	
	CE	Castro, B., et al., "Peptide Coupling Reagents VI. A Novel, Cheaper Preparation of Benzo-triazolyl-oxymethyl-(dimethylamino)phosphonium Hexafluorophosphate (BOP Reagent)," <i>Synthesis</i> , Vol. 11, pp. 751-752 (1976).	
	CF	Dick L., et al., "Degradation of Oxidized Insulin B Chain by the Multiproteinase Complex Macropain (Proteasome)," <i>Biochem.</i> , Vol. 30, pp. 2725-2734 (1991).	
	CG	Goldberg, A., "The Mechanism and Functions of AIP-Dependent Proteases in Bacterial and Animal Cells," <i>Eur. J. Biochem.</i> , Vol. 203, pp. 9-23 (1992).	
	CH	Goldberg, A. and Rock, K., "Porteolysis, Proteasomes, and Antigen Presentation," <i>Nature</i> , Vol. 357, pp. 375-379 (1992).	
	CI	Hershko, A. and Ciechanover, A., "The Ubiquitin System for Protein Degradation," <i>Annu. Rev. Biochem.</i> , Vol. 61, pp. 761-807 (1992).	
	CJ	Kettner, C. and Shenvi, A., "Inhibition of the Serine Proteases Leukocyte Elastase, Pancreatic Elastase, Cathepsin G, and Chymotrypsin by Peptide Boronic Acids," <i>J. Biol. Chem.</i> , Vol. 259, pp. 15106-15114 (1984).	
	CK	Kettner, C., et al., "Kinetic Properties of the Binding of $\alpha$ -Lytic Protease to Peptide Boronic Acids," <i>Biochem.</i> , Vol. 27, pp. 7682-7688 (1988).	

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		Application Number	Not yet Assigned		
		Filing Date	December 8, 2003		
		First Named Inventor	Julian Adams, et al.		
		Group Art Unit	N/A		
		Examiner Name	N/A		
Sheet	2	of	3	Attorney Docket Number	MPI94-008CP2DV2CN5M

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Examiner Initials*	Cite No. <sup>1</sup>	Include the name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	T <sub>2</sub>
	CL	Kinder, D. and Katzenellenbogen J., "Acylamino Boronic Acids and Difluoroborane Analogues of Amino Acids: Potent Inhibitors of Chymotrypsin and Elastase," <i>Journal of Medicinal Chemistry</i> , Vol. 28, pp. 1917-1925 (1985).	
	CM	Kinder, D., et al., "Antimetastatic Activity of Boro-Amino Acid Analog Protease Inhibitors Against B16BL6 Melanoma in Vivo," <i>Invasion Metastasis</i> , Vol. 12, pp. 309-319 (1992).	
	CN	Li, X., et al., "Isolation and Characterization of a Novel Endogenous Inhibitor of the Proteasome," <i>Biochem.</i> , Vol. 30, pp. 9709-9715 (1991).	
	CO	Lim, M., et al., "The Solution Conformation of (D)Phe-Pro-Containing Peptides: Implications on the Activity of Ac-(D)Phe-Pro-boroArg-OH, A Potent Thrombin Inhibitor," <i>Journal of Medicinal Chemistry</i> , Vol. 36, pp. 1831-1838 (June 25, 1993).	
	CP	Matteson D. and Sadhu, K., "(R)-1-Acetamido-2-phenylethaneboronic Acid. A Specific Transition-State Analogue for Cymotrypsin," <i>Journal of Am. Chemistry Soc.</i> , Vol. 103, pp. 5241-5242 (1981).	
	CQ	Murakami, K. and Etlinger, J., "Endogenous Inhibitor of Nonlysosomal High Molecular Weight Protease and Calcium-Dependent Protease," <i>Proc. Natl. Acad. Sci. USA.</i> , Vol. 83, pp. 7588-7592 (1986).	
	CR	Rechsteiner, M., "Ubiquitin-Mediated Pathways for Intracellular Proteolysis," <i>Ann. Rev. Cell Biol.</i> , Vol. 3, pp. 1-30 (1987).	
	CS	Rivett, A., "The Multicatalytic Proteinase. Multiple Proteolytic Activities," <i>Journal of Biological Chemistry</i> , Vol. 264, pp. 12215-12219 (1989).	
CT	CT	Rivett, A., "The Multicatalytic Proteinase of Mammalian Cells," <i>Arch. Biochem. Biophys.</i> , Vol. 268, pp. 1-8 (1989).	

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Sheet	3	of	3	Attorney Docket Number	MPI94-008CP2DV2CN5M

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	CU	Rock, K., et al., "Inhibitors of the Proteasome Block the Degradation of Most Cell Proteins and the Generation of Peptides Presented on MHC Class I Molecules," <i>Cell</i> , Vol. 78, pp. 761-771 (September 9, 1994).	
	CV	Sheehan, J., et al., "A Rapid Synthesis of Oligopeptide Derivatives without Isolation of Intermediates," <i>J. Am. Chem. Soc.</i> , Vol. 87, pp. 2492-2493 (1965).	
	CW	Takahashi, L., et al., "Crystallographic Analysis of the Inhibition of Porcine Pancreatic Elastase by a Peptidyl Boronic Acid: Structure of a Reaction Intermediate," <i>Biochem.</i> , Vol. 28, pp. 7610-7617 (1989).	
	CX	Tanaka, K., et al., "Proteasomes: Protein and Gene Structures," <i>New Biol.</i> , Vol. 4, pp. 173-187 (1992).	
	CY	Tsai, D., et al., "Diastereoselection in Reactions of Pinanediol Dichloromethaneboronate," <i>Organometallics</i> , Vol. 2, pp. 1543-1545 (1983).	
	CZ	Tsilikounas, E., et al., "Identification of Serine and Histidine Adducts in Complexes of Trypsin and Trypsinogen with Peptide and NonPeptide Boronic Acid Inhibitors by <sup>1</sup> H NMR Spectroscopy," <i>Biochem.</i> , Vol. 31, pp. 12839-12846 (1992).	
	CCA	Veale C., et al., "Nonpeptidic Inhibitors of Human Leukocyte Elastase. 5. Design, Synthesis, and X-Ray Crystallography of a Series of Orally Active 5-Aminopyrimidin-6-one-Containing Trifluoromethyl Ketones," <i>J. Med. Chem.</i> , Vol. 38, pp. 98-108 (January 6, 1995).	
Examiner Signature			Date Considered

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